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EXAMINER	
OLSON, ERIC	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,707	SHIMOBOJI, TSUYOSHI	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *14,15,18,19,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,16,17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted May 1, 2007 in response to a requirement for restriction made in the previous office action. This application is a national stage application of PCT/JP03/04949, filed April 18, 2003, which claims priority to foreign applications JP2002-116508, filed April 18, 2002, JP2002-209429, filed July 18, 2002, and JP2002-331551, filed November 15, 2002.

Election/Restrictions

Applicant's provisional election without traverse of group I, claims 1-13, 16, 17, 20, and 21, drawn to a hyaluronic acid:copolymer composite according to instant claim 1, filed March 1, 2007, is acknowledged. As the election was made without traverse, the requirement for restriction is made **FINAL**.

Claims 14, 15, 18, 19, 22, and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on May 1, 2007.

Claims 1-13, 16, 17, 20, and 21 are pending in this application and examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 16, 17, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Base claim 1 is drawn to a hyaluronic acid bound to a block polymer. It is not clear from the claim language or from the specification whether the claim requires that he hyaluronic acid be **covalently** bound to the block polymer or whether a hyaluronic acid that is noncovalently associated with the block polymer is included within the scope of the claims. Therefore the claims are indefinite.

Furthermore, claims 3-4 recite the phrase, "wherein said block polymer is bound to said hyaluronic acid and/or a pharmaceutically acceptable salt thereof **at only one of its two ends**." It is not clear from the claims or the specification whether this limitation "at only one of its two ends" applies to the hyaluronic acid polymer or the block polymer. Therefore the claims are indefinite.

Still further, claim 10 is drawn to a composition comprising the product of claim 1 **as its main component**. It is unclear from the claims and the specification whether the phrase "main component" is intended to mean the component present in the largest amount, or the active ingredient. Many pharmaceutical compositions contain a large amount of an inert diluent or carrier and a small amount of active agent, and the judgment as to which is the "main component" depends on how one defines that term. Therefore claim 10 is indefinite.

Finally, claim 13 is drawn to a pharmaceutical preparation **in the form of an injection**. It is not clear from the claims or the specification whether this limitation refers to any composition that could conceivably be safely injected into a subject, or only to those actually introduced into a hypodermic syringe or other apparatus for injection. Therefore claim 13 is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical preparation for treating the specific cartilage disorders recited in instant claim 12, does not reasonably provide enablement for a method of treating any joint disease whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a pharmaceutical preparation for treating joint diseases. In order for the invention to be enabled, one skilled in the art must be able to use the claimed preparation to treat any disease significantly or primarily affecting one or more joints.

The state of the prior art: Pharmaceutical preparations of hyaluronic acid are known in the art. Such compositions are known to be useful for treating damage to cartilage, such as that occurring in arthritis. They are not known to be useful for treating many other joint diseases, such as bursitis, tendonitis, carpal tunnel syndrome, herniated disks, or Charcot's joints, or diseases significantly affecting the joints such as osteonecrosis, osteoporosis, or Paget's disease of bone. As these various joint diseases arise from very different causes, there is no single treatment that is capable of treating all joint diseases.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The joints are composed of various different types of tissues, including bone, cartilage, muscle, and tendons. As a result, there are a wide variety of different disorders that can arise in the joints, involving injury, infection, autoimmunity, and abnormal tissue remodeling, among other things. Since many joint diseases do not involve cartilage (e.g. carpal tunnel syndrome or herniated disk) there is no expectation in the art that repairing cartilage will treat all joint

diseases. Therefore the attempt to treat these diseases with the specific disclosed active agent is highly unpredictable.

The Breadth of the claims: The claimed invention includes a composition that can be used to treat any joint disease. A joint disease is interpreted to be any disease whose causes or symptoms are primarily associated with any joint. (e.g. ankle, knee, hip, vertebral, shoulder, elbow, wrist, finger) Such diseases include, for example, osteoarthritis, rheumatoid arthritis, bursitis, tendonitis, carpal tunnel syndrome, torn ligaments, herniated disks, Charcot's joints, osteonecrosis, osteoporosis, and Paget's disease of bone.

The amount of direction or guidance presented: Applicant's specification discloses that hyaluronic acid injections can be used to treat joint diseases by lubricating the joint. (p. 1) This mode of action is reasonably expected to be useful for preserving cartilage against osteoarthritis, for example. The specification does not disclose any other mode of action that would be useful in treating any joint disease not involving the loss of cartilage in the joints.

The presence or absence of working examples: No working examples are provided for the treatment of any disorder.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the use of hyaluronic acid to treat all joint diseases generally. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention for the treatment of all joint diseases, one skilled in the art would have to test

the claimed invention in a wide variety of different disease models. These tests would require a significant amount of unpredictable experimentation as there is no guidance either in the prior art or in Applicant's specification for the treatment of all joint diseases using hyaluronic acid or a derivative thereof. Therefore in order to make and use the claimed invention one skilled in the art would be required to undertake an undue burden of unpredictable experimentation.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all joint diseases.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 5, 8, 10, 11, 12, 13, 16, 17, 20, and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Kim et al. (Reference included with PTO-1449, also note that

Kim et al. was first available online on February 3, 2002, as evidenced by the printout of the online citation included with the PTO-892) Kim et al. discloses a composite hyaluronic acid/Pluronic hydrogel made by covalently attaching hyaluronic acid to a polyethylene oxide / polypropylene oxide / polyethylene oxide (PEO/PPO/PEO) triblock copolymer by the carboxyl groups of HA. (p. 70, left column, last paragraph) The pluronic polymer is added at a 15:1 ratio by weight to the hyaluronic acid, leading to a ratio of much more than 8 mol %. (p. 71, left column, third paragraph) Note that the technical bulletin for Pluronic F127 (included with PTO-892) indicates that this polymer has an average molecular weight of 12.6 kD. Therefore, a 15% composition of pluronic contains 150 mg/mL, or ~1.2 μmol/mL of polymers. Since the polymer used is activated at both ends, the composition contains ~2.4 μmol/mL of polymer ends. The composition also contains 1%, or 10 mg/mL of hyaluronic acid, containing ~26 μmol/mL of carboxyl groups. Therefore, about 9% of the carboxyl groups are substituted by polymer, fulfilling the limitation of over 8% of the groups being substituted. The conjugated polymer formed a gel that underwent a phase transition at 20° in a 10% solution, with local micellization significantly altering the swelling ratio. (p. 73, right column, also Fig. 2) The gel prepared by Kim et al. is reasonably considered to be useful in for treating joint disease, assisting or treating surgical operations, and repairing tissue, thus fulfilling the limitations of claims 11, 12, 16, 17, 20, and 21. It is also reasonably considered to be in the form of an injection according to instant claim 13 as it is capable of being injected. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art. A

chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Furthermore, either the gel itself or the rHGH drug delivery system disclosed on p. 71, right column, third paragraph can be considered to be a pharmaceutical preparation according to instant claim 10. Because the drug delivery system contains only 31 mg of rHGH in 5 mL of gel, the gel is considered to be the main component of the composition.

For these reasons, Kim et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 7, 9-13, 16, 17, 20 ,and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee et al. (US patent 5470911, cited in PTO-892) in view of Schmolka et al. (Reference included with PTO-892) Rhee et al. discloses a conjugate of a glycosaminoglycan and a synthetic polymer, preferably an activated polyethylene glycol or derivative thereof having a molecular weight of 1500-20000. (column 24, lines 25-40) The glycosaminoglycan can, in one embodiment, be hyaluronic acid with from 1-5000 disaccharide subunits, or a mw of about 380-1900000. (column 7, lines 13-60)

The synthetic polymer is preferably hydrophilic and in cone embodiment is a PEO-PPO block copolymer. (column 10, lines 45-62) In one embodiment the PEG is activated at only one end, and thus will only link to the GAG at one end. (column 11, lines 27-39) These conjugates can be used as a component in various pharmaceutical compositions including compositions for injection. (column 13, line 33 – column 14, line 46) The gel prepared by Rhee et al. is reasonably considered to be useful in for treating joint disease, assisting or treating surgical operations, and repairing tissue, thus fulfilling the limitations of claims 11, 12, 13, 16, 17, 20, and 21. Rhee et al. does not disclose a conjugate in which the synthetic copolymer is PEO-PPO-PEO or PPO-PEO-PPO. Rhee et al. does not specifically teach a molecular weight of 1500000 or less for the hyaluronic acid component of the polymer.

Schmolka et al. discloses several EPO-PPO copolymers having the structure PEO-PPO-PEO or PPO-PEO-PPO. (p. 110, figures 1 and 2)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the claimed invention with the PEO-PPO-PEO or PPO-PEO-PPO triblock copolymers disclosed by Schmolka et al. and a hyaluronic acid with a molecular weight of less that 1500000. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Rhee et al. discloses that PEO-PPO copolymers generally are useful in the disclosed conjugates and because Rhee et al. discloses a range of molecular weights (380-1900000) that substantially overlaps the claimed range of under 1500000. One of ordinary skill in the art would reasonably have expected success because selecting specific embodiments of the broad teaching of the

prior art is well within the ordinary and routine level of skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-4, 7-13, 16, 17, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spaltro et al. (US patent 5490978, cited in PTO-892) in view of Schmolka et al. (Reference included with PTO-892) Spaltro et al. discloses block copolymers containing a polysaccharide moiety and a polyalkylene oxide moiety. (column 2, lines 13-57) Hyaluronic acid is listed as a suitable polysaccharide (column 3, line 28) and the polysaccharide preferably has a molecular weight of 1000-50000. (column 3, lines 21-25) Suitable polyalkylene oxides include copolymers of ethylene oxide and propylene oxide. (column 3, lines 61-64) The polymer can be endcapped, leading to a product of formula AB (A = polysaccharide, B = polyalkylene oxide) in which the polymer is attached to hyaluronic acid at only one end. (column 3, line 65 – column 4, line 8) The polyalkylene oxide suitably has a molecular weight of 1000-20000. (column 4, lines 9-17) It is noted that for the polymers of the formula AB, the polyalkylene oxide is introduced at one position into the polysaccharide. For a hyaluronic acid of less than about 5000 Da, this leads to a ratio of incorporation of the polyalkylene oxide of greater than 8 mol % per glucuronic acid. The block polymers described by Spaltro et al. are used in various pharmaceutical compositions. (column 5,

line 35 – column 8, line 17) The copolymers, either in one of the disclosed compositions or in their pure form, are reasonably considered to be pharmaceutical compositions according to the claimed invention, and are suitable for injection. They are reasonably considered to be useful in for treating joint disease, assisting or treating surgical operations, and repairing tissue, thus fulfilling the limitations of claims 11, 12, 13, 16, 17, 20, and 21, as they possess the same structure, and thus the same properties, as the claimed invention. Spaltro et al. does not explicitly exemplify a block polymer in which the hyaluronic acid is less than 1500 kD or less than 5 kD, or one in which the polyalkylene oxide is PEO-PPO-PEO or PPO-PEO-PPO having a molecular weight of 1200 daltons or more.

Schmolka et al. discloses several EPO-PPO copolymers having the structure PEO-PPO-PEO or PPO-PEO-PPO. (p. 110, figures 1 and 2)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the claimed invention with the PEO-PPO-PEO or PPO-PEO-PPO triblock copolymers disclosed by Schmolka et al. and a hyaluronic acid with a molecular weight of less that 5000. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Spaltro et al. discloses that PEO-PPO copolymers generally are useful in the disclosed conjugates and because Spaltro et al. discloses a range of molecular weights (1000-50000) that substantially overlaps the claimed range of under 1500000 or under 5000, and because furthermore the disclosed range of 1000-20000 for the polyalkylene oxide substantially overlaps the claimed range of 1200 or more. One of ordinary skill in the art would reasonably have expected

success because selecting specific embodiments of the broad teaching of the prior art is well within the ordinary and routine level of skill in the art. It has been held that it is within the skill in the art to select optimal parameters in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the invention taken as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-5, 10-13, 16, 17, 20, and 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 15 of copending Application No. 10/571005. (Published as US patent publication 20070031503, cited in PTO-892, herein referred to as '005) Although the conflicting

claims are not identical, they are not patentably distinct from each other because claims 1-7 and 15 of '005 anticipate the claimed invention. Specifically, claim 1 of '005 is drawn to a hyaluronic acid modification product comprising of a copolymer of hyaluronic acid and a polylactic acid/polyglucolic acid copolymer, anticipating instant claim 1. Claims 2-7 further define that the polymer is attached at only one end to the hyaluronic acid and is attached by a carboxyl group. Claim 15 is drawn to a drug carrier containing the HA modification product, which is reasonably considered to be a pharmaceutical composition. The product by '005 is reasonably considered to be useful in for treating joint disease, assisting or treating surgical operations, and repairing tissue, thus fulfilling the limitations of claims 11, 12, 16, 17, 20, and 21. It is also reasonably considered to be in the form of an injection according to instant claim 13 as it is capable of being injected. Any properties exhibited by or benefits provided the composition are inherent and are not given patentable weight over the prior art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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